ADVISORY ACTION

Status of the Application

[1] Claims 1-33 are pending in the application.

[2] Applicant's amendment to the claims after final rejection, filed on 9/1/10, is acknowledged and has been entered into the record. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's remarks filed on 9/1/10 in response to the final Office action mailed on 6/1/10, have been fully considered and are deemed to be persuasive to overcome at least one of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn. Rejections and/or objections previously applied to claims 34-35 are withdrawn solely in view of the instant amendment to cancel these claims.

[4] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

[5] Claims 3-4 and 7-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 3/11/09.

[6] Claims 1-2 and 5-6 are being examined on the merits.

Claim Rejections - 35 USC § 112, Second Paragraph

[7] The rejection of claims 1-2 and 5-6 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "…the amino acid sequence with the substitution…of one to five amino acids…" is withdrawn in view of the instant claim amendment to recite "…the amino acid sequence of SEQ ID NO:2 except for having substitution, deletion, insertion, addition or inversion of no more than one to five amino acids..."

Claim Rejections - 35 USC § 112, First Paragraph

[8] The written description rejection of claims 1-2 and 5-6 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection as it applied to previous claims 1-2 and 5-6 was fully explained in a prior Office action. See [14] beginning at p. 5 of the Office action mailed on 11/24/09.

RESPONSE TO ARGUMENT: Beginning at p. 19 of the instant remarks, applicant argues the rejection is obviated by the instant amendment to recite, "…the amino acid sequence of SEQ ID NO:2 except for having substitution, deletion, insertion, addition or inversion of no more than one to five amino acids..." in parts (B) of claims 1 and 5.

Applicant's argument is not found persuasive. The amendment to parts (B) of claims 1 and 5 is acknowledged. However, the examiner maintains that the specification fails to describe all members of the genus of claimed polypeptides, particularly with respect to the recited "function". While the members of the genus of recited polypeptides are structurally limited, the "function" of the genus, *i.e.,* forms a "neoculin

dimer" having a "taste-modifying activity" in claim 1(B) and can be processed to a "mature polypeptide neoculin acidic subunit" which can form a "neoculin dimer" having a "taste-modifying activity" in claim 5(B), which functions are widely variant, at least for reasons that follow. The specification fails to define "neoculin dimer", which term has been interpreted as a homodimer or a heterodimer with any other polypeptide. Also, the term "taste-modifying activity" encompasses any modification to the sense of taste including (but not limited to) salty to sweet, sweet to salty, and sweet to bitter. Further, there is no structural limitation with respect to the processing of the polypeptide of claim 5(B) to a mature "polypeptide neoculin acidic subunit".

With respect to the function of polypeptides of claim 1(B), the specification discloses only a single representative function that is correlated to the recited structure, *i.e.,* forms a heterodimer with the polypeptide of SEQ ID NO:6, the heterodimer having a sweet taste and reducing sour taste. With respect to the function of polypeptides of claim 5(B), the specification discloses only a single representative function that is correlated to the recited structure, *i.e.,* cleavage to form a polypeptide having the structural features as recited in claim 1, forms a heterodimer with the polypeptide of SEQ ID NO:6 and has a sweet taste and reduces sour taste. Other than these disclosed functions, the specification fails to disclose any other functions of a polypeptide as encompassed by the claims. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus, and thus, that the applicant was not in possession of the recited genus. The claimed

subject matter is not supported by an adequate written description because a representative number of species has not been described.

[9] The scope of enablement rejection of claims 1-2 and 5-6 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection as it applied to previous claims 1-2 and 5-6 was fully explained in a prior Office action. See [15] beginning at p. 9 of the Office action mailed on 11/24/09.

RESPONSE TO ARGUMENT: At p. 21 of the instant remarks, applicant argues the rejection is obviated by the instant amendment to recite, "…the amino acid sequence of SEQ ID NO:2 except for having substitution, deletion, insertion, addition or inversion of no more than one to five amino acids..." in parts (B) of claims 1 and 5.

Applicant's argument is not found persuasive. The amendment to parts (B) of claims 1 and 5 is acknowledged. However, the examiner maintains that the specification fails to enable the full scope of claimed polypeptides, particularly with respect to the recited "function". With respect to the term "neoculin dimer", which is undefined in the specification, it is noted the term has been interpreted as a homodimer or a heterodimer with any other polypeptide. Also, the term "taste-modifying activity" encompasses any modification to the sense of taste including (but not limited to) salty to sweet, sweet to salty, and sweet to bitter. Further, there is no structural limitation with respect to the processing of the polypeptide of claim 5(B) to a mature "polypeptide neoculin acidic subunit".

The specification discloses a single working example of an “NAS” polypeptide and a single working example of a “PNAS” polypeptide as encompassed by the claims, *i.e.,* SEQ ID NO:2 and SEQ ID NO:3, respectively. The function of SEQ ID NO:2 is disclosed as being forming a heterodimer with the polypeptide of SEQ ID NO:6, the heterodimer having a sweet taste and reducing sour taste. The function of SEQ ID NO:6 is cleavage to form SEQ ID NO:2, forming a heterodimer with the polypeptide of SEQ ID NO:6, the heterodimer having a sweet taste and reducing sour taste. However, these working examples, in combination with the remaining disclosure of the specification fail to provide the necessary guidance for making the entire scope of claimed polypeptides with recited functions as noted above. Also, the specification fails to provide guidance for altering SEQ ID NO:2 and 3 to achieve any function as broadly encompassed by the claims.

Although SEQ ID NO:2 forms a heterodimer with the polypeptide of SEQ ID NO:6, the heterodimer having a sweet taste and reducing sour taste, it is highly unpredictable as to whether or not variants of SEQ ID NO:2 or 3 as encompassed by the claims would maintain such activities. The amino acid sequence of a polypeptide determines the polypeptide’s structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence

where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.,* multiple substitutions.

It is well-known in the art that even a single amino acid alteration can alter the function of a polypeptide. See, *e.g.,* MPEP 2144.08.II.A.4.(c), which states, "[i]n the area of biotechnology, an exemplified species may differ from a claimed species by a conservative substitution ("the replacement in a protein of one amino acid by another, chemically similar, amino acid... [which] is generally expected to lead to either no change or only a small change in the properties of the protein." Dictionary of Biochemistry and Molecular Biology 97 (John Wiley & Sons, 2d ed. 1989)). The effect of a conservative substitution on protein function depends on the nature of the substitution and its location in the chain. Although at some locations a conservative substitution may be benign, in some proteins only one amino acid is allowed at a given position. For example, the gain or loss of even one methyl group can destabilize the structure if close packing is required in the interior of domains. James Darnell et al., Molecular Cell Biology 51 (2d ed. 1990)."

While methods of isolating or generating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen for any and all polypeptide variants having any function(s) as encompassed by the claims.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all polypeptides as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

[10] The rejection of claim(s) 1 and 5 under 35 U.S.C. 102(b) as anticipated by Yamashita et al. (*J. Biol. Chem.* 265:15770-15775, 1990; hereafter "Yamashita"; cited in the IDS filed on 7/28/06) is withdrawn in view of the instant claim amendment to recite, "...the amino acid sequence of SEQ ID NO:2 except for having substitution, deletion, insertion, addition or inversion of no more than one to five amino acids..." The reference of Yamashita does not *explicitly* disclose a polypeptide that comprises the amino acid sequence of SEQ ID NO:2 or a variant thereof having no more than 1-5 amino acid

modifications as encompassed by the claims. However, the examiner maintains the position that Yamashita inherently discloses such a polypeptide and claims 1 and 5 have been included in the rejection under 35 U.S.C. 102/103 below.

Claim Rejections - 35 USC § 102/103

[11] The rejection of claims 2 and 6 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Yamashita (*supra*) as evidenced by Suzuki (*FEBS Lett.* 573:135-138, 2004; cited in the IDS filed on 7/28/06; hereafter "Suzuki") and Shimizu-Ibuka et al. (*J. Mol. Biol.* 359:148-158, 2006; hereafter referred to as "Shimizu-Ibuka") is maintained for the reasons of record and the reasons set forth below. Claims 1 and 5 are reinstated in the instant rejection in view of the amendment to parts (B). As noted above, while Yamashita does not *explicitly* disclose a polypeptide that comprises the amino acid sequence of SEQ ID NO:2 or a variant thereof having no more than 1-5 amino acid modifications as encompassed by the claims, Yamashita inherently discloses such a polypeptide. The rejection as it applied to previous claims 1-2 and 5-6 was fully explained in a prior Office action. See [17] beginning at p. 16 of the Office action mailed on 11/24/09.

The reference of Yamashita teaches an extract of *Curculigo latifolia* fruit that is sweet and comprises curculin (p. 15570, column 1) and teaches isolation of curculin (p. 15770, column 2), noting that "[p]urified curculin tastes sweet" (p.15771, column 1, bottom) and "[c]urculin also has the property of modifying a sour taste into a sweet taste" (p. 15771, paragraph bridging columns 1-2).

The evidentiary references of Suzuki and Shimizu-Ibuka are relied upon as extrinsic evidence that makes clear that the missing descriptive matter is necessarily present in the thing described in the reference, *i.e.,* the isolated curculin polypeptide of Yamashita is a heterodimer of a polypeptide comprising the amino acid sequence of SEQ ID NO:2 and a polypeptide comprising the amino acid sequence of SEQ ID NO:6 and is glycosylated and that it would be so recognized by persons of ordinary skill. Put another way, the evidentiary references of Suzuki and Shimizu-Ibuka are relied upon to show that the isolated curculin of Yamashita is composed of two distinct subunits, one of the subunits being the NAS of SEQ ID NO:2 and the other being the PNAS of SEQ ID NO:6; and that the NAS subunit of the polypeptide of Yamashita is glycosylated according to claims 2 and 6.

Evidentiary reference Suzuki references curculin of Yamashita (*supra*), noting that previous studies by Yamashita suggested that curculin is a homodimer of a 114 residue polypeptide (p. 135, column 2). Suzuki discloses that curculin is actually a heterodimer of curculin1 and curculin2 subunits (which correspond to NBS of SEQ ID NO:6 and NAS of SEQ ID NO:2, respectively, as shown in Figure 1 at p. 136 of Suzuki), where *only* the curculin1-2 heterodimer exhibits sweet-tasting and taste-modifying activities, whereas the respective homodimers do not (p. 136, column 2, bottom). The amino acid sequence of curculin2 is 100% identical to SEQ ID NO:2 herein (See Appendix B sequence alignment at pp. 20-21 of the Office action mailed on 11/24/09). Since SEQ ID NO:3 is a “mature” subsequence of SEQ ID NO:2, the amino acid sequence of curculin2 is necessarily also 100% identical to SEQ ID NO:3 herein.

Similarly, evidentiary reference Shimizu-Ibuka teaches “Curculin, occurring in the fruit of *Curculigo latifolia*…was initially regarded as a homodimer consisting of two identical subunits, although the recombinant homodimer was devoid of any taste-modifying activity”, referring to the reference of Yamashita (*supra*) (p. 149, column 1, middle). According to Shimizu-Ibuka, “[a] recent study revealed that the active component is actually a heterodimeric protein, which was designated as ‘neoculin’. This protein consists of an acidic, glycosylated subunit (neoculin acidic subunit, NAS) of 113 amino acid residues…”, referring to the reference of Suzuki (*supra*).

Regarding the limitations of claims 2 and 6, according to the specification, the polypeptide isolated from the fruit of *C. latifolia* is glycosylated with an N-linked sugar chain comprising mannose/N-acetylglucosamine/fucose/xylose at a ratio of 3/2/1/1 (p. 41) and thus because curculin of Yamashita is isolated from the fruit of *C. latifolia,* it is necessarily glycosylated with an N-linked sugar chain comprising mannose/N-acetylglucosamine/fucose/xylose at a ratio of 3/2/1/1.

This anticipates claims 1-2 and 5-6 as written.

RESPONSE TO ARGUMENT: Beginning at p. 23 of the instant remarks, applicant argues the taste modifying activity of neoculin (heterodimer of SEQ ID NO:2 and SEQ ID NO:6) is "far stronger" than that of curculin (homodimer of SEQ ID NO:6), referring to Example 10 at pp. 47-49 of the substitute specification, particularly Table 5 at p. 49. Applicant argues this “far stronger” taste modifying activity is an advantage relative to curculin.

Applicant's argument is not found persuasive. The "curculin" used in the comparison is not the polypeptide of Yamashita. As noted in the prior Office action at p. 19, the "curculin" used in the noted comparison is actually a *homodimer* of a single subunit of curculin (see p. 48, middle), where evidentiary references Suzuki and Shimizu-Ibuka clearly teach curculin as isolated by Yamashita is a *heterodimer.* As such, the "curculin" used in the taste comparison is not the polypeptide of Yamashita. Rather, as evidenced by the references of Suzuki and Shimizu-Ibuka, the curculin of Yamashita is the same as the disclosed and claimed neoculin heterodimer.

There is no evidence of record that the taste modifying activity of neoculin is different from that of the sweet-tasting curculin of Yamashita. To the contrary, evidentiary reference Suzuki teaches, "[s]weet-tasting and taste-modifying activities of the recombinant curculin1-2 heterodimer are comparable with those of native curculin" (p. 136, column 2, bottom), where the recombinant curculin1-2 heterodimer appears to be identical to "neoculin".

At p. 24, applicant further argues the polypeptide of Yamashita is disclosed as a dimer of a 114 amino acid polypeptide, with an amino acid sequence that is distinct from SEQ ID NO:2, and identifies the polypeptide as "curculin". Applicant argues that this polypeptide as described by Yamashita does not teach or suggest the claimed polypeptide.

Applicant's argument is not found persuasive. The examiner acknowledges that the amino acid sequence disclosed by Yamashita at p. 15772 is distinct from that of SEQ ID NO:2. However, the amino acid sequence disclosed by Yamashita at p. 15772

is not relied upon as anticipating the claimed invention. As shown in the sequence alignment of Appendix A of the Office action mailed on 6/1/10, the amino acid sequence disclosed by Yamashita is the NBS subunit of SEQ ID NO:6 of a curculin heterodimer. Although Yamashita does not expressly disclose the NAS subunit of SEQ ID NO:2 of curculin, evidentiary references Suzuki and Shimizu-Ibuka provide establish that the NAS subunit of SEQ ID NO:2 of curculin was *necessarily* present in the curculin of Yamashita for at least the reasons presented above.

That curculin of Yamashita is not a homodimer of the Yamashita-sequenced polypeptide sequence is further supported by the disclosure by Yamashita that "[p]urified curculin tastes sweet" (p.15771, column 1, bottom) and "[c]urculin also has the property of modifying a sour taste into a sweet taste" (p. 15771, paragraph bridging columns 1-2), whereas evidentiary references Suzuki and Shimizu-Ibuka note that the homodimer of the Yamashita-sequenced polypeptide had no such activities.

That Yamashita fails to disclose the presence of the NAS subunit of SEQ ID NO:2 in the isolated curculin polypeptide is not fatal to the rejection. MPEP 2112.I makes clear that "the discovery of a previously unappreciated property of a prior art composition…does not render the old composition patentably new to the discoverer". See also MPEP 2112.II, "[t]here is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference". In accordance with MPEP 2112.IV, the examiner has provided a basis in fact and/or technical reasoning to

reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art".

See also *In re Crish*, 393 F.3d 1253, 73 USPQ2d 1364 (Fed. Cir. 2004), where the court held that the claimed promoter sequence obtained by sequencing a prior art plasmid that was not previously sequenced was anticipated by the prior art plasmid which necessarily possessed the same DNA sequence as the claimed oligonucleotides. The court stated that "just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel."

Beginning at p. 24, applicant further argues that after publication of Yamashita, JP 10-215884 and US Patent 5,395,921 also disclose a curculin polypeptide that is a homodimer. Applicant argues that in contrast to homodimeric curculin, the instant invention is a heterodimer comprising SEQ ID NO:2 and SEQ ID NO:6. According to applicant, the inventors were the first to "clarify the presence of a heterodimer in curculin", which is referred to as neoculin and has a "remarkable" taste-modifying activity.

Applicant's argument is not found persuasive. Initially, it is noted that according to 37 CFR 1.116(e), "An affidavit or other evidence submitted after a final rejection…may be admitted upon a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented". Although there appears to be no showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented", the evidence of JP 10-215884

and US Patent 5,395,921 has nonetheless been entered into the record in the interest of advancing prosecution.

Addressing the merits of applicant's argument, it is noted that there is no dispute that Yamashita discloses curculin as a homodimer. Evidentiary references Suzuki and Shimizu-Ibuka refer only to the curculin as disclosed by Yamashita (the references of JP 10-215884 and US Patent 5,395,921 are not mentioned by Suzuki and Shimizu-Ibuka) and that the initial characterization of curculin as a homodimer was not correct, rather the polypeptide expressly disclosed by Yamashita is actually one subunit of a heterodimer of polypeptides comprising SEQ ID NO:2 and SEQ ID NO:6, respectively. In view of the post-filing evidence presented by Suzuki and Shimizu-Ibuka, one of ordinary skill in the art would recognize that the missing descriptive matter, *i.e.,* SEQ ID NO:2, is necessarily present in the thing described, *i.e.,* the curculin of Yamashita. As to the taste-modifying activity of the curculin of Yamashita, as noted above, evidentiary reference Suzuki teaches that the sweet-tasting and taste-modifying activities of recombinant curculin1-2 heterodimer (which appears to be identical to neoculin), are comparable with those of native curculin (p. 136, column 2, bottom).

Beginning at p. 25, applicant further argues that in view of the various curculin "materials" as disclosed by Yamashita, JP 10-215884, and US Patent 5,395,921 and that Suzuki and Shimizu-Ibuka are not available as prior art, the teachings of Yamashita do not explicitly disclose or suggest the claimed polypeptide, nor do the teachings of Yamashita inherently disclose the claimed polypeptide.

Applicant's argument is not found persuasive. There is no dispute that Yamashita does not explicitly disclose the claimed polypeptide. Nor is there dispute that the references of Suzuki and Shimizu-Ibuka are not available as prior art. The issue is whether or not Yamashita, in view of the post-filing evidence of Suzuki and Shimizu-Ibuka, inherently discloses the claimed polypeptide. The examiner maintains that in view of the post-filing evidence presented by Suzuki and Shimizu-Ibuka, where each of the references of Suzuki and Shimizu-Ibuka specifically cites to the reference of Yamashita (the references of JP 10-215884 and US Patent 5,395,921 are not mentioned by Suzuki and Shimizu-Ibuka), one of ordinary skill in the art would recognize that the missing descriptive matter, *i.e.,* SEQ ID NO:2, is necessarily present in the thing described, *i.e.,* the curculin of Yamashita. Thus, contrary to applicant's position, one of ordinary skill in the art would recognized that the polypeptide of Yamashita necessarily comprises SEQ ID NO:2.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

At least for the reasons and the reasons set forth above, the examiner maintains the position that the claimed invention is anticipated by the reference of Yamashita.

Conclusion

[12] Status of the claims:

Claims 1-33 are pending.

Claims 3-4 and 7-33 are withdrawn from consideration.

Claims 1-2 and 5-6 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656